Indian Journal of Chemistry
Vol. 37B, February 1998, pp. 163 - 166

Note

Reaction of *N*-arylsulfonylaziridines with dimethylsulfoxonium methylide in the presence of 18-crown-6—An improved synthesis of 2-aryl-*N*-arylsulfonylazetidines

Upender K Nadir* & Anjali Arora

Department of Chemistry, Indian Institute of Technology, Hauz Khas, New Delhi 110016, India

Received 17 June 1997; accepted 21 October 1997

An improved synthesis of 2-aryl-*N*-arylsulfonyl-azetidines by the reaction of *N*-arylsulfonylaziridines with dimethylsulfoxonium methylide in the presence of 18-crown-6 is described.

Synthetic methods for azetidines, the nitrogen analogues of cyclobutane, suffer from lack of generality and low yields[1-3]. In our programme directed towards overcoming some of these difficulties, we have reported[4] earlier a synthesis of *N*-arylsulfonylazetidines, involving methylene transfer from dimethylsulfoxonium methylide to *N*-arylsulfonylaziridines. The synthesis was found to be general and afforded azetidines in 5-70% yields. The azetidines were accompanied by a `sulfoxide' and a `sulfonamide'; the former could be characterized easily, whereas the latter was not. The synthesis was stereospecific and the carbon suffering nucleophilic attack underwent inversion[5]. Also the azetidine isolated corresponded to that formed by the attack of the ylide on the unsubstituted carbon of the aziridine ring. However, the synthesis suffered from two obvious drawbacks: (i) It involved use of sodium hydride and rigorously dry solvent and reaction conditions and (ii) the yields of some of the azetidines were low[6]. The reaction procedure could be simplified and the drawback (i) was overcome by the use of a phase transfer catalyst[7]. However, it did not lead to any improvement in the yields. This has been achieved now and forms the subject of the present communication.

In order to improve the yields of the azetidines, it was considered important first to identify and characterize the side products and then suppress the reaction leading to their formation. The side product generally described as `sufonamide' has now been characterized and found to be a mixture of **4a** (major) and **4b** (minor). Its formation may be rationalized in terms of Scheme I.

The increase in the sulfoxide yield may be attributed to increasing probability of attack of DMSO on the betaine to abstract a methyl group[6], solvent being in excess.

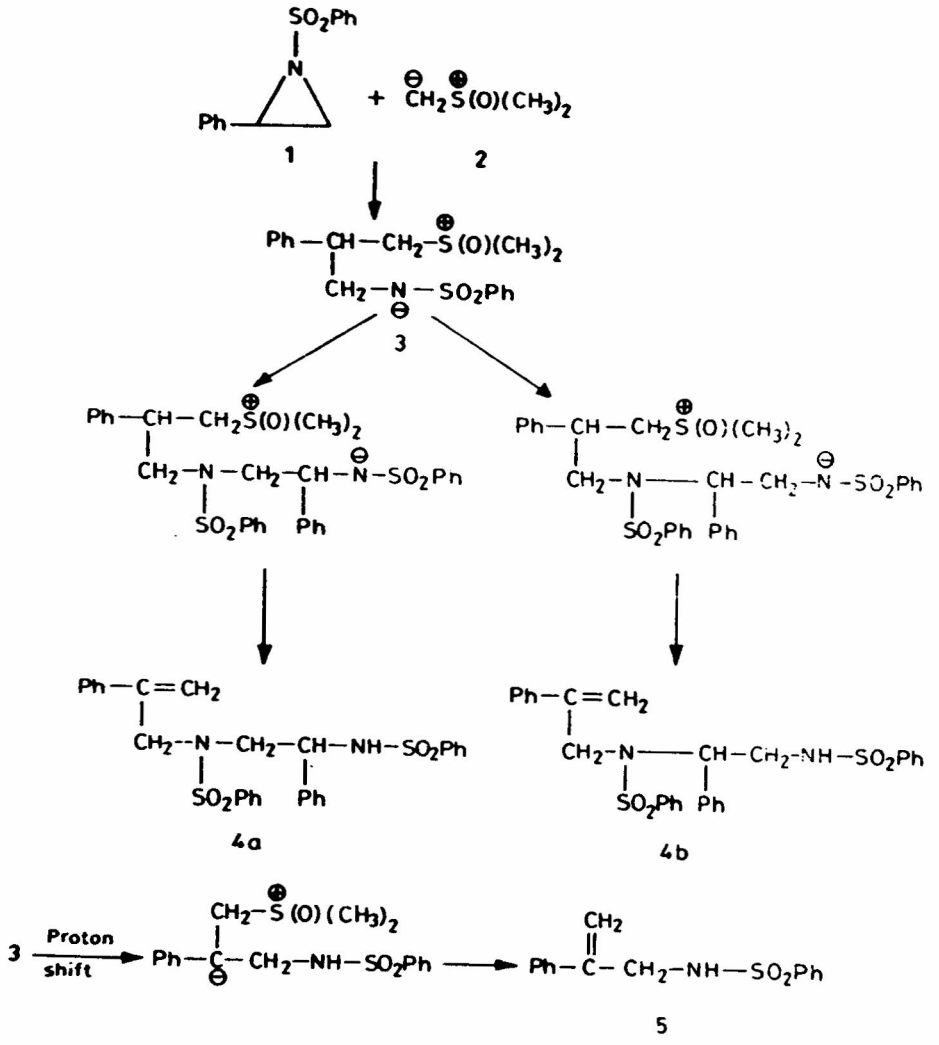
To minimize formation of these side products aziridine **1a** was subjected to various other base-solvent combinations; only with $K^+O^-Bu^t$-DMF slightly better yields were obtained. However significant improvement in the yields of azetidines **6a-f** was observed, when *N*-arylsulfonylaziridines **1a-h** were reacted with dimethylsulfoxonium methylide generated from trimethylsulfoxonium chloride and potassium-*t*-butoxide in DMF in the presence of a catalytic amount of 18-crown-6 (Scheme II, Table I).

Usefulness of crown ethers in the reactions of sulfur[8] and phosphorous ylides[9] has been reported earlier.

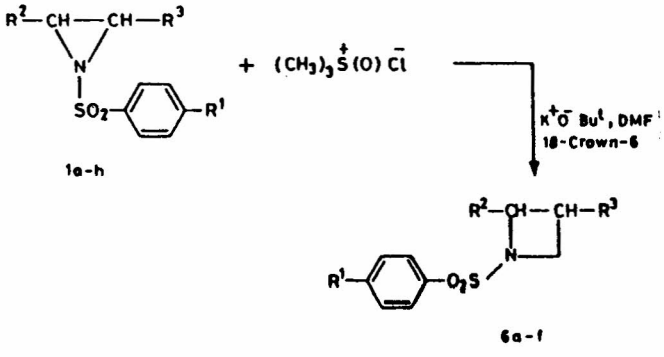
The role of 18-crown-6 in this reaction is apparently two fold. It improves the cation solvation and hence the most basic form of butoxide ion is obtained[10]. This leads to more efficient ylide formation. With the increased ylide concentration, the concentration of unattacked aziridine decreases thereby decreasing the sulfonamide formation. Secondly, it behaves as a solid-liquid phase transfer catalyst. This is inferred from the fact that the solution of trimethylsulfoxonium chloride and potassium-*t*-butoxide becomes transparently clear only on addition of 18-crown-6. Also, as observed by us earlier in other PTC reactions, the reaction proceeds more efficiently when trimethylsulfoxonium chloride is used as the salt for ylide generation. Another similarity with PTC catalyzed reactions is that both *cis*- and *trans*-2,3-diphenyl-1-benzenesulfonylaziridines (**1g and 1h**) failed to react with **2** under these conditions.

Experimental Section

All the starting *N*-arylsulfonylaziridines were prepared according to the literature procedure[6]. Trimethylsulfoxonium iodide and trimethylsulfo-



Scheme I



Scheme II

xonium chloride were prepared according to the procedure of Kuhn *et al*[11]. Melting points are uncorrected. IR spectra (KBr pellets) were recorded on Nicolet 5DX FTIR instrument; ^1H NMR and ^{13}C NMR spectra in $CDCl_3$, on JEOL FX 100 MHz and 25 MHz respectively using TMS as internal standard and mass spectra (70 ev) on JMS 300 (JEOL) GC/MS spectrometer. Anhydrous sodium sulphate was used as a drying agent.

Reaction of 2-phenyl-1-benzenesulfonylaziridine 1a with dimethylsulfoxonium methylide 2. The ylide **2**, prepared by the reaction of trimethylsulfoxonium iodide (1.30 g,3.9 mmoles) with 67% sodium hydride (0.211g, 5.9 mmoles) was reacted with aziridine **1a** (1.0g, 3.9 mmoles) for 18-20 hr at room temperature under N_2, according to the literature procedure. Work-up, followed by column chromatography on silica gel gave, on elution with benzene, azetidine **6a** (0.551 g, 51%), m.p.124-25°C (lit.[6] m.p. 123-25°C). Further elution with benzene-ethyl acetate (2:1) led to the isolation of sulfonamides **4a** (0.157 g, 15.35%) and **4b**

Table I—Percentage yields of azetidines prepared by two different methods

Aziridine	Azetidine	Substituents	Yield of the azetidine using NaH/DMSO and trimethylsulfoxonium iodide (%)	Yield of the azetidine using $K^+O^-Bu^t$/DMF and trimethylsulfoxonium chloride and catalytic amount of 18-crown-6 (%)
1a	**6a**	R^2 = Ph $R^1 = R^3$ =H	52	60
1b	**6b**	R^2= *p*-ClPh, $R^1 = R^3$ =H	17	39
1c	**6c**	R^2 = m-ClPh, $R^1 = R^3$ = H	30	44
1d	**6d**	R^2=*p*-MePh, $R^1 = R^3$ = H	20	37
1e	**6e**	R^2=*m*-MePh, $R^1 = R^3$ = H	29	34
1f	**6f**	R^2 = *m*-NO_2Ph, $R^1 = R^3$ = H	5	25
1g	**6g**	$R^2 = R^3$ = Ph, R^1 = H (*cis*)	76	—
1h	**6h**	$R^2 = R^3$ = Ph R^1 = H (*trans*)	80	—

(0.050g, 5.25%); m.pts. 111-13°C and 163-64°C respectively. (Found: C, 65.41; H, 5.22; N, 5.29. $C_{29}H_{28}N_2O_4S_2$ requires C, 65.41; H, 5.26; N, 5.26%); IR (KBr): 3400 (NH), 1647 (C=CH_2), 1339 & 1164 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) (for **4a**): δ 2.96 (dd, 1H, *J*=15Hz & 5Hz, PhCH-CH_2), 3.35 (dd, 1H, *J*=15Hz & 10Hz, PhCH-CH_2), 3.61 (d, 1H, *J*=15Hz, CH_2=C-CH_2), 4.27 (d, 1H, *J*=15Hz, CH_2=C-CH_2), 4.46 (dd, 1H, *J*=10Hz & 5Hz, Ph-C*H*-CH_2), 5.01 (s, 1H,=C<^H_H), 5.39 (s, 1H,=C<^H_H), 5.9 (d, 1H, *J*=5Hz, NH), 7.01-7.8 (m, 20H, Ar-H); ^{13}C NMR ($CDCl_3$) (for **4a**): δ 51.39 (t, *C*H_2-C=CH_2), 52.08 (t, PhCH-*C*H_2), 55.67 (d, *C*H-Ph), 117.98 (t, =*C*H_2), 126.26-142 (m, C_{arom} & C=CH_2); ^1H NMR ($CDCl_3$) (for **4b**): δ 3.47 (m, 2H, PhCH-CH_2), 3.77 (d, 1H, 17Hz, CH_2=C-CH_2), 4.37(d, 1H, *J*=17Hz, CH_2=C-CH_2), 4.63 (broad t, 1H, NH), 4.83 (t, 1H, *J*=8.5Hz, PhC*H*-CH_2), 5.13 (s, 1H, =C<^H_H), 5.29 (s, 1H, =C<^H_H), 6.7-7.8 (m, 20H, Ar-H); ^{13}C NMR ($CDCl_3$) (for **4b**): δ 44.39 (t, *C*H_2-C=CH_2), 49.42 (t, NH-*C*H_2), 60.63 (d, PhCH=CH_2), 116.72 (t, =*C*H_2), 122.26-144 (m, C_{arom} & C=CH_2).

Further elution with benzene-ethyl acetate (1:1) and extraction of aqueous layer with glacial acetic acid followed by crystallization from chloroform-pet. ether, afforded the sulfoxide, yield 0.275g (20.5 %); m.p. 135-37°C (lit.[12] m.p. 135-37°C).

Reaction of aziridine 1a with dimethylsulfoxonium methylide 2, generated from trimethylsulfoxonium iodide and sodium hydride in excess DMSO. The ylide **2**, prepared from the reaction of trimethylsulfoxonium iodide (1.30g,5.9 mmoles) with 67% sodium hydride (0.211g, 5.9 mmoles) was reacted with aziridine **1a** (1.03g, 3.9 mmoles) dissolved in 50 mL of dry DMSO for 20 hr at room temperature under N_2. Work-up by the reported procedure[6], followed by column chromatography on silica gel, gave the azetidine **6a** (eluent: benzene) (0.121g, 11.2 %), the sulfonamides **4a** & **4b** (0.107g, 10%) (eluent: benzene/ethyl acetate; 2:1) and 2-phenyl-3-benzenesulfonamido-1-propene **5** (0.135g, 12.5 %), m.p. 110-12°C (Found: C, 65.73; H, 5.51; N, 5.19. $C_{15}H_{15}NO_2S$ requires C, 65.93; H, 5.49; N, 5.13%); MS (70 ev): m/z 273 (M^+), 141 (–SO_2Ph), 170 (–CH_2NHSO_2Ph), 77 (Ph);IR (KBr): 3310 (NH), 1635 (C=CH_2), 1330 and 1164 cm^{-1} (SO_2);^1H NMR ($CDCl_3$): δ 4.03 (d, 2H, *J*=4Hz, collapses to a singlet on D_2O shake, PhC-CH_2), 4.99 (broad triplet, 1H, exchangeable with D_2O, NH), 5.27 (d, 2H, *J*=4Hz,

PhC=CH_2), 7.15-7.88 (m, 10H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 47.03 (t, CH_2-$NHSO_2Ph$), 115.15 (t, PhC=CH_2), 125.90-132.60 (m, Ar and PhC=CH_2).

Reaction of *N*-arylsulfonylaziridines with dimethylsulfoxonium methylide generated from trimethylsulfoxonium chloride and potassium-*t*-butoxide in DMF in the presence of 18-crown-6. General procedure. To a stirred solution of trimethylsulfoxonium chloride (2.74 mmoles) in dry DMF (5 mL) was added a solution of freshly prepared potassium-*t*-butoxide (2.74 mmoles) in dry DMF (5 mL) under an atmosphere of N_2. Catalytic amount of 18-crown-6 (0.05g) was introduced through a dropping funnel followed by a solution of the aziridine (1.82 mmoles) in dry DMF (25 mL). The mixture was stirred overnight, the solvent removed under reduced pressure and the residue diluted with ice-cold water (25 mL) and extracted with ether (3×25 mL). The combined ethereal extracts were washed with water (1×20 mL), dried and the solvent stripped off to leave an oil. The oil on column chromatography on silica gel gave the azetidine **6** (eluent: benzene) and the sulfonamides **4** (eluent: mixture of benzene-ethyl acetate 2:1).

Acknowledgement

Financial help from CSIR, New Delhi, India is gratefully acknowledged.

References

1 Cromwell, N H, Philips B, *Chem Rev.*, 79, **1979**, 331; Moore J A, *in Heterocyclic Compounds with three and four membered rings, Part II*, edited by A Weissberger (Interscience Publishers, New York), **1964**, 885.
2 Moore J A & Ayers R S, *in Small Ring Heterocycles*, edited by A Hassner (John Wiley & Sons, New York), 42, **1983**, 1-217.
3 Parrick J, *Prog Heterocyclic Chem*, 3, **1991**, 58.
4 Nadir U K & Koul V K, *Synthesis*, **1983**, 554.
5 Nadir U K, Sharma R L & Koul V K, *Tetrahedron*, **1989**,1851.
6 Nadir U K, Sharma R L & Koul V K, *J Chem Soc Perkin Trans* 1, **1991**, 2015.
7 Nadir U K & Arora A, *Indian J Chem*, 32B, **1993**,279.
8 Baker R & Sims R J, *Synthesis*, **1981**, 117.
9 Kajiwara T, Nakatomi T, Sasaki Y & Hatandaka A, *Agri Biol Chem*, 44, **1980**, 2099.
10 Dibase S A & Gokel G W , *J Org Chem*, 43,**1978**, 447.
11 Kuhn R & Trichmann H, *Ann*, 611, **1958**, 117.
12 Koul V K, *Studies towards the synthesis of azetidines using dimethylsulfoxonium methylide and related ylides*, Ph D Thesis, IIT, Delhi, **1983**.